IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chopp	Confirmation No.: 2465
Serial No. 10/500,694	Group Art Unit: 1609
Filed: 12/21/04	Examiner: WEBB, Walter E.

For: NITRIC OXIDE DONORS FOR TREATMENT OF DISEASE AND INJURY

Attorney Docket No: 1059.00106

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

I, Dr. Michael Chopp, being duly sworn, do hereby state that:

1. I am the inventor of the above-captioned application.

2. I am skilled in the art and have worked extensively in the field of neurology and specifically with ischemic stroke.

3. Claims 1-13 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In response thereto, as previously stated in the Response of January 4, 2008, Applicant and others have demonstrated that ischemic stroke induces neurogenesis in the adult rat and mouse (see previous Response for references). Stroke-induced neurogenesis has also recently been demonstrated in the adult human brain, even in advanced age patients. Transplantation of rodent or human mesenchymal stromal cells (MSCs) substantially enhances neurogenesis and improves neurological functions after stroke in the rat. Based on these data, I predicted that administration of MSCs promotes endogenous neurogenesis in stroke patients. Although there are no data showing that MSCs enhance neurogenesis in human patients, clinical trials in humans with stroke and spinal cord injury show that intravenous administration of bone marrow cells or direct transplantation of autologous whole bone marrow into the site of spinal cord injury improves neurological function significantly improves neurological function after stroke and spinal cord injury, respectively.

Rat models of disease are widely employed for the development of many treatments. The particular rat model used in the present invention is an *in vivo* model. It is thus accepted methodology for one skilled in the art of neurogenesis to use the rat model herein and apply results of the rat model to humans, because the results in the rat model are predictive of results in humans. Modern medical science emerges from the laboratory and from animal models of disease. While the examples of the present invention involve using the rat model, there are many instances throughout the specification when human application is described (see for example paragraphs [0044], [0054], [0057], [0083]). As a reminder, the USPTO does not have the same requirements of the FDA - there is no requirement in the USPTO that Applicant provide human data to establish enablement of the methods of the present invention. It is more than sufficient that the rat model is predictive of human results. Reconsideration of the rejection is respectfully requested.

4. Claims 1, 3, 5-8, 10, and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,075,028 to Graham. Graham does not disclose administering sildenafil to ischemic patients, but rather to Tourette's syndrome patients. The presently pending claims have been amended to require that the phosphodiesterase type 5 inhibitor is administered to ischemic patients.

The effects of sildenafil in Tourette's syndrome versus ischemia are quite different. Tourette's syndrome is a neuropsychiatric disorder. Stroke, neural injury, and certain neurodegenerative diseases are characterized by infarction – the death of brain tissue, i.e. neural damage. Tourette`s syndrome is not a form of neural damage or injury where cerebral tissue is infarcted. In Tourette`s, there are no neurological deficits and no evidence of any cell death or damage, only abnormal behavior, in sharp contrast to ischemia. The etiology and pathophysiology of Tourette's is completely different from that of ischemia. Demonstrating that sildenafil can relieve or reduce tics associated with Tourette's is completely irrelevant to reducing neurological deficits caused by infarction after ischemia. Treatment of ischemia with sildenafil evokes neurogenesis and brain remodeling, mechanisms of action which cannot be inferred by the transient amelioration of behavioral symptoms present in Tourette`s patients. In other words, one cannot in any logical way extrapolate that reduction of tics in a neuropsychiatric disease would disclose or predict neurogenesis and recovery from a cerebral infarction.

Also, Graham discloses that sildenafil transiently reduces neurological symptoms of Tourette's syndrome because the symptoms return when administration of sildenafil is ceased. Graham does not provide any mechanisms underlying the effect of sildenafil on reduction of the symptoms. Nowhere in Graham is there any statement or inference to neurogenesis in the brain and brain plasticity with relation to ischemia. The data herein demonstrate that sildenafil enhanced-neurogenesis and functional outcome persist in ischemic rats for at least 20 days after termination of the use of the drug. In addition, it is demonstrated that agents which increase cGMP levels such as sildenafil act directly on neural progenitor cells in brain to induce the production of new neural cells.

The Office Action holds that "a way of identifying increased numbers of new neurons would be to recognize improvement in the disease after administration" with respect to Tourette's syndrome. I respectfully disagree. Neurogenesis is not a "necessary" condition for improvement of function. Improvement of function is achieved in Tourette's by other methods. Thus, improvement of function, i.e. reduction of tics, after treatment of Tourette's syndrome does not in any way imply causation by neurogenesis or the presence of neurogenesis. Again, as stated above, there is no relationship between Tourettes syndrome, a disease without cerebral infarction, and ischemia (stroke), in which neurological deficits are caused by the death of cerebral tissue.

No cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, Graham cannot perform the required steps of claims 1, 8, 10, and 12 of "identifying increased numbers of new neurons", i.e. evidence of neurogenesis.

Therefore, since the Graham patent does not disclose or suggest promoting neurogenesis with a phosphodiesterase type 5 inhibitor in an ischemic patient or identifying increased numbers of new neurons as set forth in the presently pending independent claims, the claims are patentable over the Graham patent and reconsideration of the rejection is respectfully requested.

The undersigned declares further all statements made herein of his knowledge are true and that all statements made upon information and belief are believed to be true, and further that the statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 9/26, 2008

Michael Chopp
Dr. Michael Chopp